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MALNUTRITION AND QUALITY OF LIFE IN PATIENTS TREATED FOR ORAL OR OROPHARYNGEAL CANCER

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Abstract: *Background.* This study assessed whether malnourished patients score lower on quality of life after treatment for oral/oropharyngeal cancer.

Methods. Malnutrition (weight loss $\geq 10\%$ in 6 months/ $\geq 5\%$ in 1 month) and quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire) were assessed cross-sectionally in patients treated for oral/oropharyngeal cancer. The interval after treatment varied from 1 day to 3 years. The relationship between malnutrition and quality of life was analyzed univariately (Mann–Whitney *U* test) and multivariately (linear regression analyses). Statistical significance was set at $p < .05$.

Results. Prevalence of posttreatment malnutrition was 16% (18/115, 95% confidence interval [CI]: 9% to 23%). Analyzed univariately, malnourished patients scored significantly worse on physical functioning ($p = .007$) and fatigue ($p = .034$) than well-nourished patients. Multivariate analysis revealed that malnutrition was significantly related to physical functioning ($p = .015$).

Conclusions. Malnourished patients treated for oral/oropharyngeal cancer score lower on quality of life scales related to physical fitness. © 2010 Wiley Periodicals, Inc. *Head Neck* 33: 490–496, 2011

Keywords: malnutrition; weight loss; oral cancer; oropharyngeal cancer, quality of life

Malnutrition has been defined as a subacute or chronic state of nutrition, in which a combination of undernutrition (insufficient food intake) and inflammation leads to a decrease in muscle mass, fat mass, and diminished body function (ie, immune function,

cognitive function, and muscle strength).¹ In this definition, body function includes muscle function, cognitive function, and immune function. In the period before treatment, prevalence of malnutrition in patients with head and neck cancer ranges from 19% to 57%.^{2–4} Patients with oral or oropharyngeal cancer are at risk for malnutrition as the result of oral symptoms caused by either the tumor localization or sequelae of treatment (see Figure 1). Furthermore, inflammatory activity may contribute to malnutrition, either indirectly as a result of undernutrition or directly mediated by the tumor or treatment.^{1–3}

Malnutrition is associated with increased morbidity and mortality. Malnutrition may result in an increased complication rate, including impaired wound healing, reduced immune function, and decreased tolerance to surgery, radiotherapy, and chemotherapy.^{4–6} Additionally, malnutrition has a negative impact on disease-related quality of life.⁷ Although cancer stage is the major determinant of patients' overall quality of life, the impact of malnutrition combined with insufficient food intake on quality of life has been shown to be more important than the stage of the disease process.⁸

The negative influence of malnutrition on quality of life has already been demonstrated in patients with head and neck cancer in the period before, during, and shortly after treatment.^{9–12} However, heterogeneous populations regarding tumor localization were studied and follow-up was limited to 6 months after treatment. Consequently, the relationship between malnutrition and quality of life in the long-term period after treatment for oral or oropharyngeal cancer remains unclear. Therefore, the aim of our study was to test the hypothesis that in the period after treatment for oral or oropharyngeal cancer,

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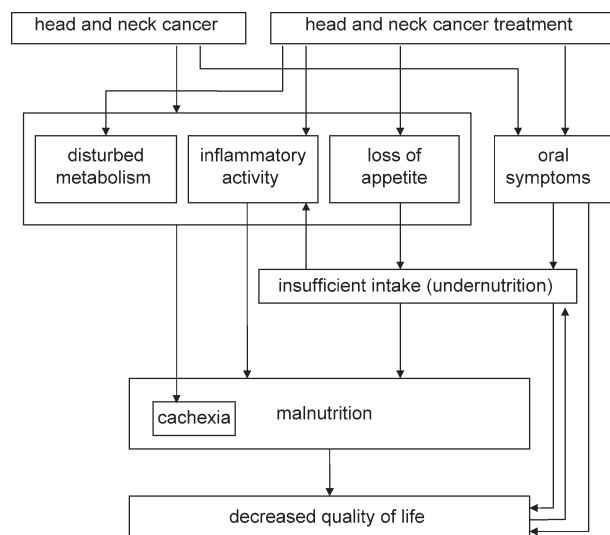


FIGURE 1. Causes and consequences of malnutrition in patients with head and neck cancer (modified after Soeters et al¹). Malnutrition in patients with head and neck cancer may be caused by both cancer itself and its treatment. Cancer may be accompanied by disturbed metabolism, inflammatory activity, and loss of appetite. These factors combined may cause cachexia, a sub-type of malnutrition. Furthermore, the localization of the tumor may cause oral symptoms that hamper food intake. Treatment-related oral symptoms, such as swallowing problems, chewing problems, dry mouth, and changes in smell and taste may hinder food intake as well, possibly resulting in insufficient food intake. Malnutrition may result in decreased quality of life.

malnourished patients experience a lower quality of life than that of well-nourished patients.

MATERIALS AND METHODS

A convenience sample of 185 consecutive adult patients was asked to participate in the study between October 2004 and February 2006. These patients had been treated for oral or oropharyngeal cancer within the setting of the multidisciplinary head and neck cancer group of the University Medical Center Groningen (UMCG), The Netherlands. Patients willing to participate underwent assessment after their scheduled visit to the physician. The study was approved by the Ethics Committee of the UMCG. Informed consent was obtained from all participants.

In this cross-sectional study, nutritional status and quality of life were assessed once after head and neck treatment. The interval between day of assessment and last day of head and neck cancer treatment varied from 1 day to 3 years. Patients were classified into 3 groups based on the interval between end of treatment and time of study measurement: 0 to 3 months after treatment; >3 to 12 months after treatment; and >12 to 36 months after treatment. Inclusion criteria were a completed head and neck cancer treatment, ability to speak the Dutch language, and capable of completing a questionnaire. Treatment

modalities were surgery (local tumor excision and/or neck dissection), surgery followed by radiotherapy, radiotherapy alone (either a conventional fractionated or accelerated scheme), or radiotherapy with concomitant chemotherapy (carboplatin and 5-fluorouracil). Exclusion criteria were patients with a recurrent, residual, or newly diagnosed tumor within 3 months after study measurement; patients with edema as a result of liver, kidney, or cardiac disease, to prevent influence of comorbidities on hydration status; and patients with uncontrolled diabetes mellitus, to prevent possible confounding in risk factors for weight loss.

All patients were routinely referred to a dietitian working at the UMCG. Patients received dietary counseling at time of diagnosis, during admission for surgery, and weekly during radiotherapy. Duration of dietary counseling after treatment was generally limited to the first half year after treatment. During dietary counseling, nutritional requirements were estimated: 30 or 35 kcal and 1.0 or 1.5 gram protein per kg actual body weight for well-nourished and malnourished patients, respectively.¹³ For patients with a body mass index (BMI) >27 ($n = 37$), a body weight equivalent to BMI = 27 was calculated and used in the calculations, to correct for the relatively lower metabolic active muscle mass in overweight patients.¹⁴

Diagnosis and treatment information were retrieved from medical records and included the number of primary tumors, localization of each primary tumor, size of each primary tumor, tumor type of the last primary tumor, number and type of head and neck cancer treatment(s) the patient had undergone, and dates of start and ending of each treatment. Pretreatment body weight (ie, body weight at start of treatment) was retrieved from the medical records as well.

Assessment of Nutritional Status. Actual body weight (kilogram) was measured on a calibrated Seca 701 scale (Medical Scales and Measuring Systems Seca Ltd, Birmingham, UK). Patients were allowed to eat and drink before assessment. Patients were measured in indoor clothing without shoes, after voiding the bladder. Either 1 kg (for light clothes) or 1.5 kg (for jeans and sweater) was deducted from the measured weight, and this corrected weight was used for further analysis. This weight is referred to as post-treatment body weight. Patients were asked for their normal body weight (without clothes and shoes), ie, body weight at 1 and 6 months before study measurement. Height was measured by a stadiometer (Seca 222, Medical Scales and Measuring Systems Seca Ltd).

Percentage weight loss was calculated as: $[(\text{normal body weight} - \text{actual body weight}) / \text{normal body weight}] \times 100$. Malnutrition was defined as weight loss $\geq 10\%$ in 6 months or $\geq 5\%$ in 1 month.^{4-6,15-17}

BMI (kg/m^2) was calculated as actual body weight/ (body height²).

Quality of Life Assessment. Quality of life was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire (EORTC QLQ-C30).¹⁸ This self-rating questionnaire contains 30 items, including 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), a global health scale, and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties). In addition, the EORTC head and neck module (EORTC QLQ-H&N35) was used to assess pain in mouth or throat, swallowing problems, senses problems, dry mouth, sticky saliva, trouble with social eating, and trouble with social contact. Missing data were imputed in accord with the guidelines in the manual.¹⁹ Linear transformation to “0–100” scales were carried out in accord with the EORTC QLQ-C30 scoring manual.¹⁹ For the functioning scales and the global quality of life scale a high score represents a better level of functioning. For the symptom scales and the single-item questions a high score represents a high level of problems.

In addition, 3 questions regarding chewing problems were asked: (1) How much difficulty did you experience while eating solid food (like meat/hard bread)? (2) How much difficulty did you experience while eating dry food (like cookies)? (3) How much difficulty did you experience while eating soft food (like soft bread)? Possible answers to the additional questions were: (1) no difficulty; (2) little difficulty; (3) much difficulty; and (4) so much difficulty that eating was impossible. Answers (3) and (4) were dichotomized to “chewing problems” and answers (1) and (2) to “no chewing problems.” The timeframe for all questions was the week prior to assessment.

Dental status was considered poor if: patients were edentate without prosthesis or edentate plus prosthesis in upper or lower jaw, or had 1 edentulous jaw without prosthesis and 1 to 16 elements in the other jaw; otherwise, dental status was considered acceptable.

Maximal mouth opening was measured 3 times using 2 calibrated calipers, 1 for edentates or partially dentate patients wearing their prosthesis and 1 for edentates not wearing their prosthesis. Trismus was defined as mean mouth opening ≤ 35 mm.^{20,21}

Statistical Analysis. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 16.0 for Windows software (SPSS Inc., Chicago, IL). The interval after treatment (months) was categorized into 0 to 3 months after treatment, >3 to 12 months after treatment, and >12 to 36 months after treatment. Differences in sex, tumor size, and type of treatment (surgery alone vs radiotherapy, surgery and

radiotherapy, or chemoradiation) and interval after treatment (0–3 months after treatment, >3–12 months after treatment, and >12–36 months after treatment) between malnourished and well-nourished patients were univariately analyzed by chi-square test. Differences in age between malnourished and well-nourished patients were analyzed by independent samples Student's *t* test. Scores on the EORTC scales and items were compared between malnourished and well-nourished patients by Mann–Whitney *U* test.

The relationship between malnutrition and quality of life was analyzed in linear regression analyses. Scales of the EORTC QLQ-C30 that were related to malnutrition were entered as outcome variables. The relationship between the EORTC scales and cancer treatment was explored in a regression analysis using 3 dummy variables: (1) chemoradiation (yes, no); (2) radiotherapy (yes, no); and (3) surgery and radiotherapy (yes, no). In this way surgery alone was the “reference” therapy. Cancer treatment did not contribute significantly to the regression equation. Therefore type of cancer treatment was dichotomized into: radiotherapy, yes (including radiotherapy, surgery and radiotherapy, or chemoradiation) and no (surgery).

In the final regression analyses, malnutrition (malnutrition vs no malnutrition), sex (male vs female), age (years), tumor size (T1/T2 vs T3/T4), radiotherapy (yes, no), interval after treatment (months), pain in mouth or throat, swallowing problems, senses problems, dry mouth, sticky saliva, trouble with social eating, trouble with social contact, chewing problems (yes, no), poor dental status (yes, no), and trismus (yes, no) were entered as predictors in the linear regression analyses (stepwise backward method): entry criterion $p \leq .05$ and removal criterion $p > .10$. In all analyses, statistical significance was set at $p < .05$.

RESULTS

Patients. Of the 185 eligible patients, 63 declined participation. Reasons to decline participation were: not interested in the study (33%, 23/63), fatigue (14%, 9/63), time investment too long (17%, 11/63), or unknown reason (32%, 20/63). In total, 121 patients were included in the study. Six patients had to be excluded because of either still being under treatment ($n = 1$), tumor recurrence shortly after inclusion ($n = 1$), or not being able to undergo nutritional assessment ($n = 4$). Data of malnutrition and quality of life were complete in 115 patients. Characteristics of these 115 patients are shown in Table 1. Data of the 115 patients were used in the various analyses, unless stated otherwise. Of 115 in this study, 26 of these patients (23%) had previously been treated for a primary tumor in the head and neck region.

Nutritional Assessment. Overall, prevalence of posttreatment malnutrition was 16% (18/115, 95% confidence interval [CI]: 9% to 23%). In the periods 0

Table 1. Patient characteristics.	
Factor	No. of patients (%) [*]
Age, (mean SD), y	59.5 (11.6)
Sex	
Male	71 (62)
Female	44 (38)
Last treated tumor	
SCC	102 (89)
Salivary gland tumor	10 (9)
Other	3 (3)
T classification of last treated tumor	
T1	53 (46)
T2	33 (29)
T3	3 (3)
T4	13 (11)
Unknown	13 (11)
Site of last treated tumor	
Oral cavity	81 (70)
Oropharynx	30 (26)
Other [†]	4 (3)
Treatment of last tumor	
Surgery	61 (53)
Surgery + radiotherapy	35 (30)
Radiotherapy	12 (10)
Chemoradiation	7 (6)
Interval between end of treatment and assessment, median (IQR), mo	4.2 (1.4; 12.6)

Abbreviations: SCC, squamous cell carcinoma; IQR, interquartile range.

^{*}Sum of percentages may be dissimilar to 100% because of rounding.

[†]Neck metastasis, maxillary sinus, unknown primary.

to 3 months, >3 to 12 months, and >12 to 36 months after treatment, prevalence of malnutrition reduced from 25% (13/53) to 13% (4/32) and 3% (1/30), respectively ($p = .009$). Prevalence of malnutrition was significantly higher in patients treated with primary radiotherapy, surgery plus radiotherapy, or chemoradiation (24%, 13/54), compared with patients treated with surgery alone (8%, 5/61, $p = .037$).

Pretreatment body weight and BMI data were available for all patients. Body weight declined from 78.7 ± 13.4 kg pretreatment to 76.0 ± 14.0 kg posttreatment (mean difference, -2.8 ± 5.9 kg, $p < .001$). Mean percentage decline in pretreatment and posttreatment body weight was $3.4 \pm 7.3\%$, and no significant differences in percentage decline in pretreatment body weight between the 3 intervals after treatment were found ($p = .220$). Pretreatment BMI declined from 26.3 ± 4.0 to 25.4 ± 4.0 kg/m² posttreatment ($p < .001$).

No significant differences were found in age, sex, and tumor size (T1/T2 vs T3/T4) between malnourished and well-nourished patients.

Quality of Life. Analyzed univariately, median score of malnourished patients on global health status/quality of life was lower (66.7) than that of well-nourished patients (83.4), but this difference did not reach statistical significance ($p = .061$). Median scores of malnourished patients on physical functioning ($p = .007$) and fatigue ($p = .034$) were significantly lower than those of well-nourished patients. Median scores, interquartile ranges, and p values on the EORTC QLQ-C30 of malnourished and well-nourished patients are presented in Table 2.

Analyzed multivariately, malnutrition, treatment with radiotherapy, dry mouth, and trouble with social eating were significantly related to physical functioning ($p < .05$; Table 3). Malnutrition was not significantly related to fatigue in the multivariate linear regression analysis.

DISCUSSION

Our study is the first to assess the relationship between malnutrition and quality of life, assessing both the short-term and long-term period after

Table 2. Scores on EORTC QLQ-C30 of malnourished and well-nourished patients.

Scale or item (n)	Malnourished patients (n = 18)		Well-nourished patients (n = 97)		p value [†]
	Median	IQR	Median	IQR	
EORTC QLQ-C30					
GHSQOL (113)	66.7	50.0; 83.3	83.3	66.7; 91.7	.061
Physical functioning (115)	60.0	40.0; 80.0	100.0	60.0; 100.0	.007
Role functioning (115)	66.7	50.0; 100.0	100.0	66.7; 100.0	.106
Emotional functioning (114)	83.3	64.6; 100.0	91.7	75.0; 100.0	.221
Cognitive functioning (114)	83.3	62.5; 100.0	100.0	83.3; 100.0	.079
Social functioning (113)	91.7	62.5; 100.0	100.0	83.3; 100.0	.326
Fatigue (115)	33.3	19.4; 55.6	22.2	0.0; 33.3	.034
Nausea/vomiting (115)	0.0	0.0; 4.2	0.0	0.0; 0.0	.354
Pain (115)	25.0	0.0; 50.0	0.0	0.0; 33.3	.062
Dyspnea (115)	0.0	0.0; 33.3	0.0	0.0; 8.3	.219
Insomnia (115)	0.0	0.0; 41.7	0.0	0.0; 33.3	.630
Loss of appetite (115)	0.0	0.0; 41.7	0.0	0.0; 0.0	.236
Constipation (115)	0.0	0.0; 33.3	0.0	0.0; 0.0	.245
Diarrhea (115)	0.0	0.0; 0.0	0.0	0.0; 0.0	.251
Financial difficulties (112)	0.0	0.0; 8.3	0.0	0.0; 0.0	.449

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire; GHSQOL, General Health Survey-Quality of Life; IQR, interquartile range.

Note: (n), number of valid observations.

[†]Analyzed by Mann-Whitney U test, where bold type indicates significance.

Table 3. Results of multivariate linear regression analysis (stepwise backward) to predict scores on EORTC QLQ-C30 scales.

EORTC scale/Predictor	β	SE β	95% CI	<i>p</i> value
Physical functioning				
Malnutrition*	-15.0	6.1	-27.1, -3.0	.015
Treatment including radiotherapy†	14.6	4.9	4.9, 24.3	.004
Dry mouth	-0.2	0.1	-0.3, -0.03	.021
Trouble with social eating	-0.3	0.1	-0.6, -0.1	.003
Constant	86.8	3.4	80.1, 93.6	<.001
Fatigue				
Dry mouth	0.2	0.1	0.09, 0.3	.001
Pain in mouth or throat	0.4	0.1	0.2, 0.6	<.001
Trouble with social contact	0.6	0.1	0.03, 0.9	<.001
Constant	4.0	3.1	-2.2, 10.2	.203

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questionnaire.

Note: β , regression coefficient; SE β , standard error of β ; 95% CI, 95% confidence interval.

*Yes = 1; no = 0.

†Yes (including radiotherapy, surgery and radiotherapy, or chemoradiation) = 1; no (surgery) = 0.

treatment for oral or oropharyngeal cancer. Whereas malnutrition was already established as an important determinant of quality of life in patients with head and neck cancer in the period before, during, and shortly after treatment,⁹⁻¹² it was still unclear how malnutrition relates to quality of life in the long-term period after head and neck cancer treatment. Furthermore, the relationship between malnutrition and quality of life in patients treated for oral or oropharyngeal cancer in particular was unknown, given that previous studies were performed in heterogeneous head and neck cancer populations in which only a small number of patients with oral or oropharyngeal cancer were included.^{11,12} The current study showed that malnutrition significantly pointed toward a worse physical functioning in patients treated for oral or oropharyngeal cancer.

The lower score of malnourished patients on physical functioning in our study is considered clinically relevant because the difference in score on physical functioning between malnourished and well-nourished patients was ≥ 10 points.²² The relationship between malnutrition and physical functioning has been previously reported in other studies with respect to patients with head and neck cancer. In a prospective observational study in patients with head and neck cancer treated with surgery, surgery and radiotherapy, and radiotherapy or chemoradiation, malnourished patients scored clinically relevant, but not significantly worse on physical functioning compared to well-nourished patients, 6 months after end of treatment.¹² Another study in patients with head and neck cancer treated with radiotherapy demonstrated a significant positive effect of intensive dietary counseling on physical function, whereas in patients not receiving intensive dietary counseling physical functioning deteriorated significantly.¹¹ The relationship between malnutrition and physical functioning can be ascribed

to decreased muscle mass and muscle function. In malnourished patients, atrophy of mainly type II muscle fibers results in muscle fatigue and an altered pattern of muscle contraction and relaxation.²³

Although in our study the prevalence of malnutrition was significantly higher in the period 0 to 3 months after treatment compared to longer periods after treatment, the relationship between malnutrition and physical functioning was not confounded by interval after treatment. Interval after treatment was not significantly related to physical functioning in the multivariate linear regression analysis. However, the low prevalence of malnutrition in the long-term period after treatment indicates that malnutrition is not a factor affecting quality of life in the long-term period after treatment for oral or oropharyngeal cancer.

Besides malnutrition, treatment with radiotherapy, dry mouth, and trouble with social eating were shown to be related to physical functioning in the multivariate linear regression analysis as well. Unfortunately, dry mouth and trouble with social eating are direct and usually long-lasting sequelae of head and neck cancer treatment and are difficult to treat.²⁴ However, in contrast to these problems, malnutrition can be treated effectively, for example by intensive dietary counseling, including advice on liquid dietary supplements,¹¹ and/or tube feeding by a percutaneous endoscopic gastrostomy.²⁵

Analyzed univariately, malnutrition was significantly related to fatigue. However, when analyzed multivariately, no significant relationship between these variables was found. Dry mouth, pain in the mouth or throat, and trouble with social contact appeared to be more strongly related to fatigue than malnutrition was.

Although we found a clinically relevant worse score of malnourished patients on global health status/quality of life, this difference did not reach statistical significance. One study found a significant relationship between malnutrition and global health status/quality of life, both during and after treatment for head and neck cancer.¹² Other studies in this patient group focused on the impact of intensive dietary counseling during radiotherapy on quality of life. These studies demonstrated a positive effect of intensive dietary counseling on global health status/quality of life.^{10,11} Because in our study prevalence of malnutrition was highest shortly after treatment, it is unlikely that coping strategies played a role in the lack of a significant relationship between malnutrition and global health status/quality of life. The lack of statistical significance may be the result of insufficient power, attributed to the relatively low prevalence of malnutrition.

The results of our study indicate that a subgroup of patients does not sufficiently gain weight to pretreatment level, given the $3.4 \pm 7.3\%$ decline in pretreatment and posttreatment body weight. Prospective studies are needed to examine if such a failure to gain

weight in the long-term period after treatment for oral or oropharyngeal cancer affects quality of life and increases the risk for late complications.

Unfortunately, a gold standard for the assessment of malnutrition does not currently exist.²⁶ Weight loss is 1 of the criteria commonly used for assessment of malnutrition.¹⁷ Weight loss of $\geq 10\%$ in 6 months or $\geq 5\%$ in 1 month is a generally accepted cutoff for clinically relevant weight loss. Such a weight loss is associated with increased morbidity, such as impaired wound healing and reduced immune function.^{27,28} Besides that, weight loss of $\geq 10\%$ in 6 months or $\geq 5\%$ in 1 month has shown to be of great prognostic value in the occurrence of major postoperative complications and has been associated with higher mortality.^{4-6,27,29,30} The cutoff point used was adopted by the American Society for Parenteral and Enteral Nutrition to define "nutritionally at risk adults".¹⁵

Health-related quality of life is a complex, multidimensional concept that reflects the psychological, physical, and social effects of disease and its therapy.³¹ In addition to age, sex, tumor localization, tumor size, and treatment modality, emotional status, smoking and alcohol consumption, marital status, and income are also known to influence overall health-related quality of life in patients with oral or oropharyngeal cancer.³² In the current study, we did not measure lifestyle and socioeconomic variables, which may have acted as confounders in the relationship between malnutrition and quality of life. As a result, the relationship between malnutrition and quality of life might be overestimated.

The current study has some limitations. The first drawback is the modest participation rate of 66%. In 14% of the patients not willing to participate in this study, fatigue played a major role. For this reason, it cannot be excluded that fatigue was the result of malnutrition. Furthermore, 32% of nonparticipants did not report a reason for no participation. Since patients in the current study were informed and recruited after they had finished treatment, we speculate that patients in this phase of treatment were less motivated to participate in studies that they deemed no longer had a clear benefit for themselves. Furthermore, there is still a general belief among patients that only underweight patients may suffer from malnutrition. Because most of the patients were not underweight, these patients may have believed that participation in the current study was not relevant. Consequently, the modest participation rate may have resulted in underestimation of prevalence of malnutrition.

The second limitation is the use of a cross-sectional study design. Because patients were assessed only once after treatment, individual pre-illness scores on quality of life are unknown. Therefore, in the chosen study design we limited our analysis to test interindividual differences after treatment. Prospective studies are needed to confirm or to refute our findings. In addition, the use of a cross-sectional study design did not

allow us to identify cause-effect relationships. Previous prospective studies have demonstrated a positive relationship between deterioration of nutritional status and impairment of quality of life.^{11,12} Thus, we assume that malnutrition is more likely to be the cause than the consequence.

In conclusion, the results of our study indicate that malnourished patients score lower on quality of life scales related to physical fitness, especially in the period shortly after treatment.

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